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Allometric Scaling of Brain Regions to Intra-Cranial Volume: An Epidemiological MRI Study

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Abstract: There is growing evidence that sub-structures of the brain scale allometrically to total brain size, that is, in a non-proportional and non-linear way. Here, scaling of different volumes of interest (VOI) to intra-cranial volume (ICV) was examined. It was assessed whether scaling was allometric or isometric and whether scaling coefficients significantly differed from each other. We also tested to what extent allometric scaling of VOI was introduced by the automated segmentation technique. Furthermore, reproducibility of allometric scaling was studied different age groups and study populations. Study samples included samples of cognitively healthy adults from the community-based Age Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik Study) ($N = 3{,}883$), the Coronary Artery Risk Development in Young Adults Study (CARDIA) ($N = 709$), and the Alzheimer's Disease Neuroimaging Initiative (ADNI) ($N = 180$). Data encompassed participants with different age, ethnicity, risk factor profile, and ICV and VOI obtained with different automated MRI segmentation techniques. Our analysis showed that (1) allometric scaling is a trait of all parts of the brain, (2) scaling of neo-cortical white matter, neo-cortical gray matter, and deep gray matter structures including the cerebellum are

Additional Supporting Information may be found in the online version of this article.

[†]Some data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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significantly different from each other, and (3) allometric scaling of brain structures cannot solely be explained by age-associated atrophy, sex, ethnicity, or a systematic bias from study-specific segmentation algorithm, but appears to be a true feature of brain geometry. *Hum Brain Mapp 38:151–164, 2017.*

Key words: MRI; allometry; intra-cranial volume; brain; cortex; striatum; white matter; thalamus; AGES-Reykjavik; ADNI; CARDIA

INTRODUCTION

Since the development of (semi)-automated segmentation techniques for brain MRI, a large body of literature has emerged comparing brain volumes of different groups of people in order to find measurable traits distinctive or predictive for certain diseases. Having a good understanding of the physiologic variation in brain geometry is indispensable to discover pathological patterns. Human brain size varies considerably and different adjustment methods are applied to reduce noise stemming from this variation. Despite widespread use of standardization techniques, adjusting for intra-cranial volume (ICV) or total brain volume (TBV) when analyzing VOI is complex and controversial. In volumetric studies, ratios of VOI to ICV or TBV, or linear regression-based methods are commonly used. However, a critical evaluation of these techniques showed that each of these adjustment methods unmasks different types of relationships and results in different magnitude of effects [O'Brien et al., 2011; Voevodskaya et al., 2014]. In morphometric studies linear or non-linear stereotaxic registration of brain MR images are often used. A critical evaluation of these techniques showed that spatial transformation of MR brain images may result in significant opposite group level differences or different proportionality of brain regions compared with those obtained in native space [Allen et al., 2008]. Moreover, whether it is necessary to apply head-size adjustment in all types of comparative brain studies was evaluated in a study that investigated the effect of head size on several metrics of the brain, that is, total brain volume, VOI, cortical thickness, and voxel-based morphometry (VBM). It was concluded that head size adjustment should be considered in all volumetric and VBM studies, but not in cortical thickness studies [Barnes et al., 2010].

Probably, part of the inconsistencies in results obtained with different head/brain size adjustment methods can be explained by differences in underlying assumptions of these methods regarding preservation of proportionality of VOI to TBV across the total range of brain size variation in the population. Some techniques, such as ratio-based methods or linear registration, assume isometry of the brain, i.e. proportionality of VOI to TBV is preserved. Other techniques, such as linear regression-based methods or non-linear registration, allow for allometry to occur in case proportionality is not preserved. Although, these different theoretical underpinnings have been recognized [O'Brien et al., 2011] and caution is called when choosing the adjustment method, it is uncertain whether allometrical scaling is true feature of brain geometry.

Some previous studies have provided evidence for allometric scaling of VOI to overall brain size. One study found larger proportions of cerebral WM and smaller proportions of GM in larger TBV compared with lower TBV [Luders et al., 2002]. Another study that focused on the necessity of head size, age and gender adjustment in MRI studies, found nonlinear relationships of cortical GM, hippocampus and putamen to ICV with a power less than 1 [Barnes et al., 2010]. Other neo-cortical metrics such as cortical thickness, total surface area, and sulcal depth have also been found to scale differently from what would be predicted based on ICV in case of isometry [Im et al., 2008]. Moreover, a recent study examined power law relationships of deep GM structures and many cortical GM regions and found most of them to have non-linear relationship with ICV. Some cortical areas had a power law larger than 1 and others smaller than 1. It was also tested whether prediction error of a statistical model would decrease when ICV correction was based on power-proportion method compared with the commonly used ANCOVA method. Prediction errors with use of power proportion method were slightly lower for structures that had strong non-linear relationships to ICV [Liu et al., 2014].

Although, non-linearity and non-proportionality in scaling of some VOI to ICV have been reported, results are heterogeneous and little is known on scaling of especially deep GM regions (striatum and thalamus) and cerebellum. Also, it has not been investigated whether scaling coefficients of different brain structures are significantly

Abbreviations

ADNI	Alzheimer's Disease Neuroimaging Initiative
AGES-Reykjavik	Age Gene/Environment Susceptibility-Reykjavik Study
CARDIA	The Coronary Artery Risk Development in Young Adults Study
GM	gray matter
ICV	intra-cranial volume
MRI	magnetic resonance imaging
MTL	medial temporal lobe
TBV	total brain volume
WM	white matter

different from each other. Here, scaling of volumes of frontal, parieto-occipital and temporal cortical GM, cortical WM, medial temporal lobe (MTL), striatum, thalamus, and cerebellum with ICV was studied using automatically segmented MRI brain scans of a large sample of community dwelling older adults ($N = 3,883$) who participated in AGES-Reykjavik study. First, we investigated whether and to what extend VOI showed allometric scaling to ICV. Second, we estimated whether scaling coefficients of different VOI were significantly different from each other. Third, we studied whether scaling was similar in different age groups of our sample. Fourth, we set up an experiment to test whether the automated segmentation pipeline of AGES-Reykjavik Study could give rise to allometrical scaling. Fifth, because allometric scaling would have considerable influence on head/brain size adjustment methods, the fit of the allometric model on the volumetric data was compared with the linear model. And lastly, since the AGES-Reykjavik study population consisted of older Icelandic individuals, extrapolation of our results to groups of younger individuals and/or different ethnicity was potentially limited. Therefore, supportive analyses were conducted in two other samples (CARDIA and ADNI) that differed in mean age, source population, and method of automated MR segmentation to estimate brain volumes.

MATERIALS AND METHODS

General Design of the AGES-Reykjavik Study

The general design and demographics of the AGES-Reykjavik have been described elsewhere [Harris et al., 2007]. The population-based sample of the AGES-Reykjavik consisted of 5,764 men and women, born between 1907 and 1935. Participants underwent extensive clinical evaluation, including cognitive function testing and brain MRI. All participants signed an informed consent. The AGES-Reykjavik was approved by the Intramural Research Program of the National Institute on Aging, the National Bioethics Committee in Iceland (VSN00-063), the Icelandic Data Protection Authority, and the institutional review board of the U.S. National Institute on Aging, National Institutes of Health.

AGES-Reykjavik: MRI Acquisition and Automated MRI Segmentation

MRI was performed at the Icelandic Heart Association on a single study dedicated 1.5-T GE Signa Twinspeed EXCITE system MRI scanner. The image protocol, described previously [Sigurdsson et al., 2012], included a T1-weighted 3D spoiled gradient echo (TE 8 ms; TR 21 ms; FA 30°, FoV 240 mm; matrix 256 × 256; 110 slices; slice thickness 1.5 mm), a FSE PD/T2 (TE1 22 ms; TE2 90 ms; TR 3,220 ms; echo train length 8; FA 90°, FoV 220 mm; matrix 256 × 256; slice thickness 3.0 mm), and a FLAIR (TE 100 ms; TR 8,000 ms; inversion time 2,000 ms; FA 90°, FoV 220 mm; matrix 256 × 256; slice thickness 3.0 mm).

A fully automated segmentation pipeline was developed based on the Montreal Neurological Institute processing pipeline [Sigurdsson et al., 2012; Zijdenbos et al., 2002]. The pipeline used a multispectral approach to segment voxels into global tissue classes [cerebrospinal fluid (CSF), GM, WM, and white matter hyperintensities (WMH)]. Following this, a regional parcellation pipeline—atlas-based segmentation method—was developed to obtain volumes of different sub-structures of the brain.

Determination of VOI

The regional tissue segmentation pipeline parcellated the brain in 56 different regions (Supporting Information, Appendix A). However, for the present study, we combined regions into a limited amount of 8 VOI known to differ in gross cyto-architectural features. We separately assessed scaling of neo-cortical GM and WM to investigate in further detail the previously reported proportional changes as function of TBV. Three regions of neo-cortical GM were investigated: frontal (comprising of orbito-frontal and pre-frontal GM, precentral gyrus, cingulated gyrus, insula, and fornix), temporal (comprising of lateral temporal GM, parahippocampal, and fusiform gyrus), and parieto-occipital GM. Cortical WM volume was studied in total and included all lobar WM, corpus callosum, internal and external capsule, and WMH. The medial temporal lobe (MTL), striatum, thalamus, and cerebellum were separately studied because of their importance in many studies to neurodegenerative processes. MTL included amygdala and hippocampus (including CA regions I-IV, fimbria, and subiculum of the hippocampus). Striatum included the nucleus accumbens, caudate nucleus, putamen, and globus pallidus. The thalamus included also the hypothalamus. The cerebellum included cerebellar GM and WM. Left and right hemispheres of each structure were combined. Total brain volume (TBV) was calculated as the sum of the neo-cortical GM and WM, MTL, striatum, thalamus, brainstem, and cerebellum. ICV was defined as the sum of TBV and CSF.

Quality Control of Tissue Classification and Validation of VOI

The quality of the segmentation of the eight composite VOI was mostly dependent on the performance of the global tissue segmentation into GM, WM, WMH, and CSF, and for a small part dependent on the definition of topographical borders by the regional parcellation pipeline. Performance of both global tissue segmentation and regional tissue parcellation was evaluated. The quality control of global tissue classification consisted of three steps described in [Sigurdsson et al., 2012]. In summary these were: (1) Visual inspection of the segmentation of 14 a priori selected slices of each subject ($N = 4,356$), which

led to additional manual editing in 43 cases and rejection of 53 cases. (2) Comparison of automated versus manual global tissue segmentation of 5 preselected slices across the brain (including a slice located at the junction of the thalamus and subthalamic structures for reviewing segmentation of the deep gray matter nuclei) in 20 randomly selected cases. Resulting dice similarity index scores [Zijdenbos et al., 1994] were 0.82, 0.82, and 0.83 for GM, WM, and CSF respectively. (3) Reproducibility of the entire process of MRI acquisition and postprocessing was evaluated by repeated scanning and segmentation (four times in total) of 32 participants. Excellent intra-class correlation for all global tissue was found ($r > 0.98$, for all). Because the present study relies for an important part on good quality of ICV segmentation, the performance of the automated pipeline was further evaluated specifically on ICV. ICV was manually segmented on the same 20 brain scans used for step 2 of the quality control. Two researchers with extensive neuroradiological experience and blinded for the results of the automated segmentation, segmented ICV on axial 3D T1 weighted images, with correction and editing in sagittal and coronal planes. Resulting ICV were correlated to ICV obtained by the automated pipeline. Pearson's correlation was 0.97 (0.93–0.99) and Bland–Altmann plot showed a small overestimation of ICV of 31 cm^3 on average by the automated segmentation, but no proportional error (Supporting Information, Appendix B and C).

Performance of regional parcellation pipeline was validated against four complete manually labeled scans. Dice similarity index scores per studied region were; frontal GM: 0.83, temporal GM: 0.83, parieto-occipital GM: 0.81, striatum: 0.83, MTL: 0.80, thalamus: 0.92, cerebellum: 0.92, white matter: 0.86.

Statistical Analysis

All statistical analyses were performed with SAS v 9.13 (SAS Institute Inc., Cary, NC, USA) and all graphs were generated with R v 3.1.2 (R Core Team [2014]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/).

Analytical sample of AGES-Reykjavik study

MR scanning was performed on consenting MR eligible participants, between 2002 and 2006. From the total AGES-Reykjavik sample of 5,764 participants, 4,726 underwent successful MRI scanning. Global and regional segmentations were successful in 4,613 MR scans. We excluded cases of dementia ($N = 202$) and MCI ($N = 422$), assumed to have higher rates of atrophy, and cases for which cognitive function had not been assessed ($N = 106$). Our final study sample consisted of 3,883 people with successful brain MRI and segmentation of the images. Demographics and brain structure volumes of the AGES-Reykjavik study population were compared between women and men with *t*-tests for continuous variables and chi-square tests for categorical variables. All VOI were normally distributed.

Estimation of scaling coefficients of different VOI

Allometric coefficients of VOI with ICV were calculated using the general equation for allometric analyses, $\log(y) = \log(b) + \alpha \log(x)$, where x is ICV, y VOI, $\log(b)$ intercept, and α represents the allometric coefficient [Harvey, 1982], that is, the slope of the regression between log (ICV) and log (VOI). A coefficient greater than 1.0 is considered a positive allometric coefficient, that is, VOI increased with a power greater than 1 relative to ICV. A coefficient smaller than 1.0 is seen as a negative allometric coefficient, that is, VOI increased with a power less than 1 relative to ICV.

We chose ICV, instead of TBV, as measure of brain volume to avoid a possible bias toward isometry in estimating allometric coefficients of large VOI. Large structures occupy large volumes in TBV making the range of possible deviations from isometry smaller; this may produce an overestimate of coefficients toward 1 and reduce the ability to estimate allometric coefficients deviant from 1 [Deacon, 1990]. With the use of ICV none of the structures studied comprised more than 24% (WM) of ICV. Another important reason was that ICV is regarded as a marker for brain volume at its maximum size and therefore a marker of "pre-morbid" brain size. At time of scanning, brains of most study participants experienced more or less atrophy due to aging or pathological processes. These are factors we can largely control for in our statistical analyses, whereas it is more difficult to control for differences between current TBV without taking into account the original size of the brain at maximum. Log-transformed VOI were plotted against log transformed ICV (Fig. 1). For each VOI, allometric coefficients with ICV were calculated adjusted for age and sex, ($\log(\text{VOI}) = \text{intercept} + \alpha \log(\text{ICV}) + \beta_{age} \times \text{age} + \beta_{sex} \times \text{sex}$) and tested against the isometric scaling law of 1:1.

Comparison of allometric scaling coefficients of different VOI

Allometric coefficients of the different VOI to ICV were compared using a marginal model (PROC MIXED SAS procedure [SAS Institute Inc., Cary, NC] with repeated statement and unstructured correlation matrix), which takes into account the correlations between the VOI. The log transformed VOI were entered as dependent variables and log transformed ICV as independent variable. Interactions of log(VOI) with log(ICV) were entered in the model as a cross product together with log(ICV), log(VOI), age, and sex. The model was also run with additional independent variables [year of birth, height, achievement of higher education (highschool diploma or above], presence of infarct(s) yes/no, and contrast-to-noise ratio (CNR) between GM and WM and CNR between GM and cerebro-spinal fluid), but these did not exert significant

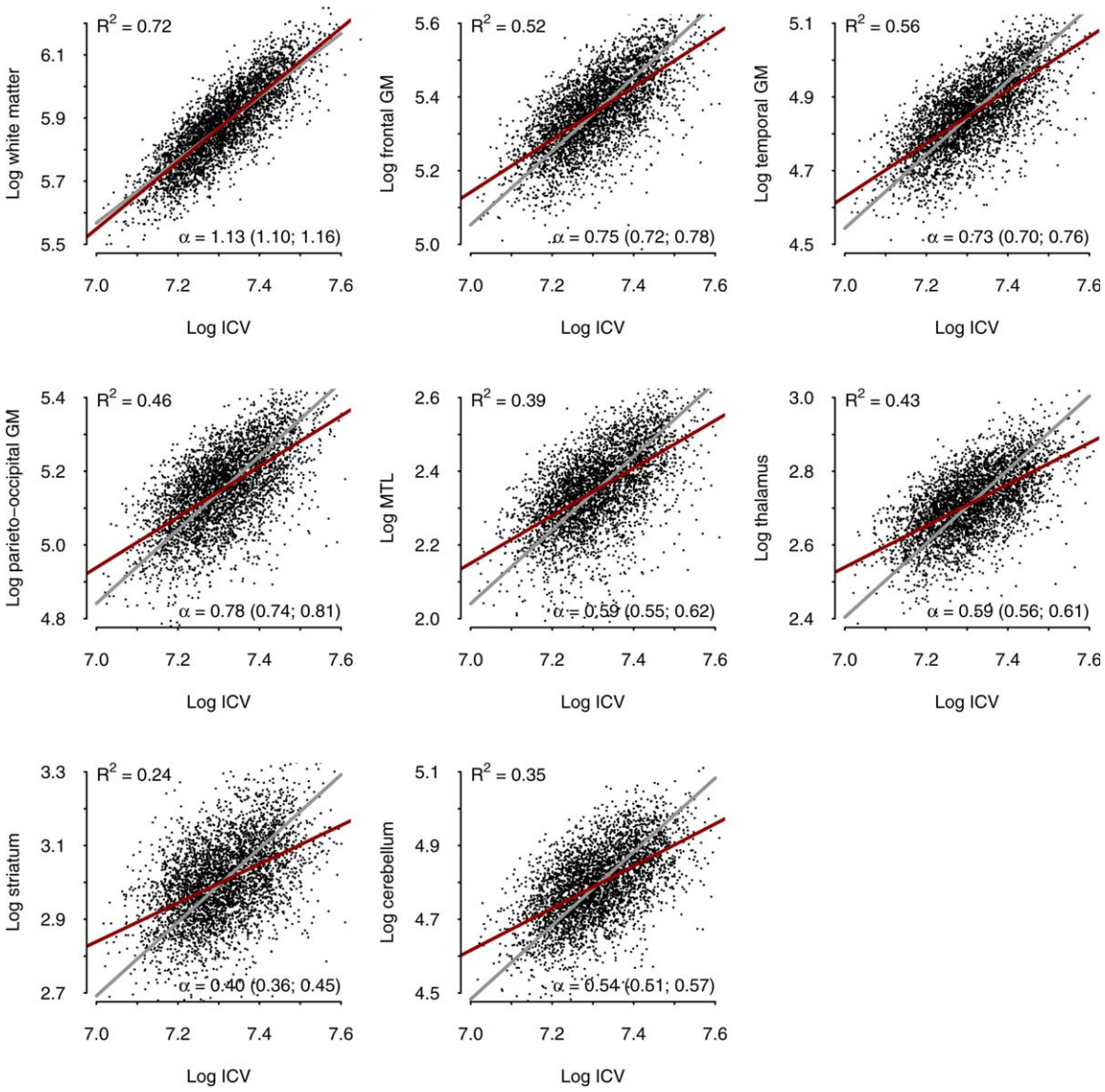

Figure 1.
Allometric coefficients of VOI with ICV. Gray line, isometry line; Red line, line of allometric log–log model between ICV and VOI.

effects and were omitted to keep the model parsimonious. A Bonferroni correction was applied to adjust for multiple testing (number of comparisons between slopes in the three mixed models = 85) and a *P*-value <0.00059 (=0.05/85) was considered significant. The analysis was performed in the entire sample and repeated for women and men separately. The numerical results of the marginal model are reported in Table II.

Allometric scaling of VOI in different age groups

To assess whether age influenced scaling of VOI with ICV, scaling coefficients of VOI to ICV were calculated for each quartile of age; the age range of the youngest quartile being 66–71 years, and of subsequent quartiles being, 72–75, 76–79, and 80–95 years. The coefficients were compared among the quartiles by testing whether there was an interaction between the quartiles and ICV.

Testing the automated segmentation pipeline with artificially linearly scaled data

To test whether a potential systematic error in the automated segmentation pipeline could introduce allometry in the volumetric data of AGES-RS, artificially linearly scaled brain scans were entered into the pipeline and the output

was investigated for allometry. Scans of a relatively small (1,402 cm^3) and relatively large brain (1,756 cm^3) were skull stripped and linearly scaled by factors ranging from 0.75 to 1.25 of its original size with steps of 0.01. The resulting sets of scaled images were subsequently processed through the AGES-Reykjavik pipeline. Log transformed volumes of the global tissues GM, WM, and CSF were plotted against log transformed ICV and α-coefficients were calculated.

Comparison of allometric model and linear regression model

The fit of the allometric model of the relationship of each VOI to ICV on the data was compared with a linear regression model. The line of prediction from the allometric model and linear model were superimposed in the same graph and R^2 of each model was calculated. Both models were conducted with adjustments for age and sex.

Allometric scaling in different study populations; supportive analyses in datasets of CARDIA and ADNI

Supportive analyses were conducted in datasets of CARDIA and ADNI. In both samples the allometric coefficients of VOI with ICV were calculated, corrected for age and sex, and tested against the isometric scaling law of 1:1, similar to the first part of analysis conducted in the AGES-Reykjavik data.

The multicenter prospective cohort CARDIA study was designed to examine the development and determinants of clinical and subclinical cardiovascular disease and its risk factors. Between 1985 and 1986, 5,115 black and white men and women (aged 16–30) were recruited from four urban sites across the United States and underwent eight examination cycles [Friedman et al., 1988]. All participants provided written informed consent at each exam, and institutional review boards from each study site and the coordinating center annually approved the study. In 2010–2011, 3,498 (72%) of the surviving cohort attended a 25-year follow-up exam. As part of this exam, a subsample of the cohort participated in the CARDIA Brain sub-study, designed to investigate the morphology, pathology, physiology and function of the brain with MRI. Exclusion criteria at the time of sample selection, or at the MRI site, were a contra-indication to MRI or a body size that was too large for the MRI scanner. Of those who were eligible for the sub-study, 719 individuals received whole brain MRI scans. Post-scan image processing was performed by the Section of Biomedical Image Analysis (BIA), Department of Radiology, University of Pennsylvania. MRI scans were inspected and passed through a quality control process. Based on previously described methods [Davatzikos, et al. 2003; Goldszal, et al. 1998; Lao, et al. 2008; Shen, et al. 2002; Zacharaki, et al. 2008], an automated algorithm was used to segment MRI structural images of supratentorial brain tissue into GM, WM, and cerebrospinal fluid. GM and WM were further characterized and segmented as 92 anatomic ROIs in each hemisphere, from which summary VOIs used in the current study were calculated. ICV was calculated as the sum of all supratentorial structures, but not infratentorial.

Some data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center, and University of California—San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1,500 adults, ages 55–90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2, and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

For the supportive analysis of our study we used volumetric brain measures derived from the standardized 1.5 T MRI screening dataset in cognitively healthy subjects that was collected between August 2005 and October 2007 and processed using FreeSurfer software (Freesurfer Software Site. Cortical Reconstruction and volumetric segmentation, (http://surfer.nmr.mgh.harvard.edu/; 2016 [accessed 07.26.16]).

RESULTS

Characteristics AGES-Reykjavik Sample

The AGES-Reykjavik sample had a mean age of 75.7 (standard deviation = 5.2) years, of which 59.8% were women. ICV ranged from 1,116 to 2,162 cm^3; 1,116 to 1,868 cm^3, in women and 1,232 to 2,162 cm^3 in men. Women had on average lower educational level ($P < 0.0001$),

TABLE I. General characteristics of the study sample

Mean (SD)[a]	All (*N* = 3,883)	Women (*N* = 2,307)	Men (*N* = 1,576)	*P*[b]
Age [years]	75.7 (5.2)	75.6 (5.3)	75.8 (5.1)	0.27
Higher education, % (N)	12.2 (473)	6.52 (150)	20.6 (323)	<0.0001
BMI [kg/m^2]	27.0 (4.3)	27.2 (4.7)	26.8 (3.7)	0.003
Diabetes, % (N)	11.1 (430)	8.76 (202)	14.5 (228)	<0.0001
Smoking status, % (N)				
Never	41.7 (1,619)	53.2 (1,226)	24.9 (393)	
Former	44.5 (1,728)	34.8 (803)	58.7 (925)	<0.0001
Current	13.8 (534)	12.0 (276)	16.4 (258)	
Alcohol intake, % (N)				
Never took alcohol	21.5 (829)	29.3 (671)	10.1 (158)	
Formerly drinking	10.8 (418)	7.78 (178)	15.3 (240)	<0.0001
Currently drinking	67.7 (2,608)	62.9 (1,440)	74.6 (1,168)	
Stroke, % (N)	28.9 (1,123)	23.5 (541)	36.9 (582)	<0.0001
ICV [cm^3]	1,502.5 (147.4)	1,422.7 (104.6)	1,619.2 (120.8)	<0.0001
TBV [cm^3]	1,045.5 (98.1)	1,004.7 (80.3)	1,105.3 (90.8)	<0.0001
WM [cm^3]	359.7 (44.6)	341.5 (36.6)	386.4 (41.8)	<0.0001
Frontal GM [cm^3]	214.5 (22.1)	207.1 (19.2)	225.3 (21.7)	<0.0001
Temporal GM [cm^3]	128.9 (13.1)	124.1 (11.1)	135.8 (12.7)	<0.0001
Parieto-occipital GM [cm^3]	173.7 (19.0)	168.7 (16.9)	181.1 (19.4)	<0.0001
Thalamus [cm^3]	15.1 (1.4)	14.7 (1.2)	15.8 (1.3)	<0.0001
MTL [cm^3]	10.6 (1.1)	10.2 (1.0)	11.1 (1.1)	<0.0001
Striatum [cm^3]	20.3 (2.3)	19.5 (2.0)	21.3 (2.2)	<0.0001
Cerebellum [cm^3]	121.3 (12.0)	117.4 (10.6)	126.9 (11.7)	<0.0001

BMI, body mass index; ApoE, apoE genotype; ICV, intra-cranial volume; TBV, total brain volume; WM, sum of neo-cortical white matter; Frontal GM, frontal neo-cortical gray matter; Temporal GM, temporal neo-cortical gray matter; Parieto-occipital GM, parietal and occipital neo-cortical gray matter; MTL, medial temporal lobe.

[a]Or else if otherwise stated.

[b]Difference between men and women from t-test for continuous variables and chi-square test for categorical variables.

higher BMI ($P = 0.003$), were diagnosed less often with diabetes ($P < 0.0001$), and had smoked ($P < 0.0001$) and drank alcohol ($P < 0.0001$) more sparingly compared with men. Women had lower means of ICV and all VOI compared with men ($P < 0.0001$) (Table I).

Allometric Scaling Coefficients of All VOI

All VOI scaled non-isometrically to ICV (Fig. 1). After correction for age and sex, a positive allometric coefficient of 1.14 (95% confident interval = 1.11–1.17)) was estimated for WM volume and negative allometric coefficients were found for frontal GM [0.76 (0.73–0.79)], temporal GM [0.75 (0.72–0.78)], parieto-occipital GM [0.79 (0.76–0.83)], MTL [0.60 (0.56–0.64)], thalamus [0.59 (0.56–0.62)], striatum [0.41 (0.37–0.45)], and cerebellum [0.55 (0.52–0.59)]. All were found significantly differently from 1 [1:1 scaling law to ICV ($P < 0.0001$)].

Significant Scaling Differences between VOI

Results from the marginal model showed that the α-coefficient of WM volume to ICV was significantly different from the α-coefficients of all GM VOI (Table II) in the entire sample, and in women and men separately. The α-coefficients of the different neo-cortical GM areas to ICV were not significantly different from each other in women and men separately. Also, the α-coefficients of MTL, thalamus, and cerebellum were not significantly different from each other in women and men separately. However, in the entire sample the α-coefficient of the MTL was not significantly different from the α-coefficient of the parieto-occipital GM, but was significantly different from the thalamus and the cerebellum. The α-coefficient of the striatum was significantly different from all other α-coefficients except for the α-coefficient of the thalamus and cerebellum in the entire sample, and the α-coefficient of the cerebellum in men only.

Allometric Scaling in Different Age Groups

The α-coefficients of VOI to ICV for each quartile of age are shown in Table III. The α-coefficients of the both cortical and deep GM structures and cerebellum in the older quartiles appeared somewhat lower compared with the younger quartiles and the α-coefficient of WM appeared higher in the older quartiles. However, these differences were non-significant, except for temporal GM which was

TABLE II. Comparison α-coefficients of different VOI to ICV, random effects mixed model

VOI	α-coefficient (95%CI)	*P*-values from comparison α-coefficients						
		WM	Frontal GM	Temporal GM	Par-occip GM	MTL	Thalamus	Cerebellum
All *N* = 3,883[a]								
WM	1.09 (1.06–1.11)							
Frontal GM	0.740 (0.714–0.766)	<0.0001						
Temporal GM	0.750 (0.724–0.774)	<0.0001	**0.34**					
Par-occip GM	0.712 (0.683–0.741)	<0.0001	**0.009**	**0.002**				
MTL	0.672 (0.642–0.702)	<0.0001	<0.0001	<0.0001	**0.02**			
Thalamus	0.588 (0.563–0.613)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001		
Cerebellum	0.598 (0.570–0.627)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	**0.48**	
Striatum	0.552 (0.518–0.586)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	**0.02**	**0.01**
Women *N* = 2,307								
WM	1.14 (1.11–1.18)							
Frontal GM	0.748 (0.709–0.787)	<0.0001						
Temporal GM	0.724 (0.687–0.762)	<0.0001	**0.15**					
Par-occip GM	0.776 (0.732–0.819)	<0.0001	**0.12**	**0.01**				
MTL	0.591 (0.543–0.639)	<0.0001	<0.0001	<0.0001	<0.0001			
Thalamus	0.590 (0.553–0.627)	<0.0001	<0.0001	<0.0001	<0.0001	**0.97**		
Cerebellum	0.552 (0.508–0.596)	<0.0001	<0.0001	<0.0001	<0.0001	**0.18**	**0.11**	
Striatum	0.380 (0.325–0.434)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Men *N* = 1,576								
WM	1.11 (1.07–1.16)							
Frontal GM	0.761 (0.713–0.809)	<0.0001						
Temporal GM	0.742 (0.696–0.787)	<0.0001	**0.33**					
Par-occip GM	0.787 (0.731–0.843)	<0.0001	**0.24**	**0.07**				
MTL	0.589 (0.532–0.645)	<0.0001	<0.0001	<0.0001	<0.0001			
Thalamus	0.582 (0.536–0.627)	<0.0001	0.0004	<0.0001	<0.0001	**0.81**		
Cerebellum	0.523 (0.469–0.577)	<0.0001	<0.0001	<0.0001	<0.0001	**0.07**	**0.04**	
Striatum	0.431 (0.367–0.495)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	**0.01**

WM, sum of neo-cortical white matter; Frontal GM, frontal neo-cortical gray matter; Temporal GM, temporal neo-cortical gray matter; Par-occip GM, parietal and occipital neo-cortical gray matter; MTL, medial temporal lobe.
[a]*P*-value from log-log mixed model adjusted for age and sex.
Bold figures represent non-significant *P*-values (>0.00059) after Bonferroni correction.

TABLE III. Comparison α-coefficients of VOI to ICV of different quartiles of age

VOI	α-coefficients for quartile of age (95% CI)				
	QI [66–71 yrs]	QII [72–75 yrs]	QIII [76–79 yrs]	QIV [80–95 yrs]	*P*[a]
WM	1.05 (1.01–1.09)	1.04 (1.00–1.08)	1.09 (1.04–1.14)	1.06 (1.02–1.11)	0.4
Frontal GM	0.74 (0.70–0.79)	0.71 (0.66–0.75)	0.72 (0.67–0.77)	0.66 (0.62–0.71)	0.11
Temporal GM	0.77 (0.73–0.81)	0.72 (0.68–0.76)	0.73 (0.68–0.78)	0.65 (0.61–0.70)	0.004
Par-occip GM	0.71 (0.66–0.76)	0.66 (0.61–0.71)	0.69 (0.63–0.75)	0.66 (0.61–0.72)	0.5
MTL	0.67 (0.62–0.72)	0.66 (0.61–0.71)	0.63 (0.57–0.69)	0.60 (0.54–0.66)	0.32
Thalamus	0.58 (0.53–0.62)	0.55 (0.51–0.59)	0.56 (0.51–0.61)	0.55 (0.51–0.60)	0.76
Striatum	0.56 (0.50–0.62)	0.52 (0.46–0.57)	0.53 (0.46–0.60)	0.48 (0.42–0.55)	0.38
Cerebellum	0.58 (0.53–0.63)	0.57 (0.52–0.62)	0.57 (0.51–0.62)	0.55 (0.50–0.61)	0.9

VOI, volume of interest; yrs, years; WM, sum of neo-cortical white matter; Frontal GM, frontal neo-cortical gray matter; Temporal GM, temporal neo-cortical gray matter; Par-occip GM, parietal and occipital neo-cortical gray matter; MTL, medial temporal lobe.
[a]Linear regression with VOI as dependent variable and ICV, quartile of age, and their interaction. *P*-value from the interaction term between ICV and quartile of age.

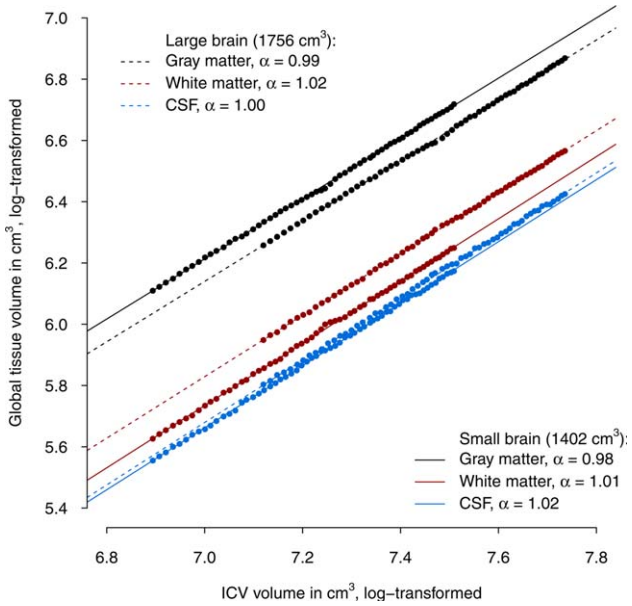

Figure 2.
Accuracy of automated segmentation pipeline; scaling of artificially linearly scaled data.

significantly lower in the older quartiles compared with the younger (*P*-value of 0.004).

Little Allometry Introduced by Automated Segmentation Pipeline

Figure 2 displays log of global tissue volumes plotted against log ICV obtained by the automated segmentation pipeline based on the artificially linearly scaled data set of a relatively large and small brain. The α-coefficients were 0.99 for GM, 1.02 for WM, and 1.00 for CSF for dataset based on the relatively large brain and 0.98 for GM, 1.01 for WM, and 10.2 for CSF for the dataset based on the relatively small brain. Because of the almost perfect fit of the points and the regression line these α-coefficients were significantly different from the isometric scaling law of 1.0 (all *P*-values < 0.0001), except for the CSF in the large brain (Table IV).

Comparable Fit of Allometric Model and Linear Regression Model

Figure 3 superimposes the line of prediction of the allometric model (and associated α-coefficient and R^2) with line of prediction of the linear model (and associated β-coefficient and R^2). Compared with the R^2 of the linear model, the R^2 of the allometric model was a few per mille smaller for cerebellar, cortical and deep GM structures and a few per mile larger for WM. The models have a comparable fit and can substitute each other.

Allometric Scaling in CARDIA and ADNI

The CARDIA sample consisted of individuals with a mean age of 50 (3.5) years, of which 52.9% were women. ICV in the CARDIA sample, including only supratentorial areas, varied from 999 to 1,643 cm^3. The ADNI sample consisted of individuals with a mean age of 76 (5.0) years, of which 49.4% were women. ICV in the ADNI sample varied from 1,116 to 1,985 cm^3. We found the highest allometric coefficients for WM volume in both CARDIA ($\alpha = 1.05$) and ADNI ($\alpha = 1.00$). All GM areas had negative allometric coefficients with the lowest coefficients in the deep GM areas (Table III). Roughly, results suggest similar trends compared

TABLE IV. Comparison of α-coefficients in study populations of AGES-Reykjavik, ADNI, and CARDIA

	AGES (*N* = 3,883)		ADNI (*N* = 180)		CARDIA (*N* = 709)	
VOI	Volume M (SD)	α (R^2)	Volume M (SD)	α (R^2)	Volume M (SD)	α (R^2)
ICV	1,502.5 (147)	NA	1,532 (156)	NA	1,208 (133)[a]	NA
TBV	1,045.5 (98)	NA	1,000 (101)	NA	983 (107)[a]	NA
WM	359.7 (44)	1.13 (0.72)	443 (57)	1.00 (0.67)	462 (59)	1.05 (0.84)
Frontal GM	214.5 (22)	0.75 (0.52)	159 (16)	0.72 (0.59)	197 (22)	0.90 (0.76)
Temporal GM	128.9 (13)	0.73 (0.56)	122 (13)	0.81 (0.67)	156 (17)	0.91 (0.73)
Parieto-occipital GM	173.7 (19)	0.78 (0.46)	114 (12)	0.81 (0.60)	124 (14)	0.94 (0.79)
Thalamus	15.1 (1.4)	0.59 (0.39)	12 (1.4)	0.76 (0.53)	14 (1.5)	0.50 (0.26)
MTL	10.6 (1.1)	0.59 (0.43)	9.9 (1.2)	0.49 (0.31)	10 (1.1)	0.61 (0.36)
Striatum	20.3 (2.3)	0.40 (0.24)	20 (2.2)	0.62 (0.30)	20 (2.1)	0.59 (0.48)
Cerebellum	121.3 (12)	0.54 (0.35)	123 (12)	0.50 (0.36)	NA	NA

Volumes are displayed in cm^3. AGES, Age, Gene, Environment/ Susceptibility-Reykjavik Study; ADNI, Alzheimer's Disease Neuroimaging Initiative; CARDIA, Coronary Artery Risk Development in Young Adults Study; Volume M (SD), mean volume in cm^3 (standard deviation); α, allometric coefficient derived from [log (VOI), intercept + α log (VOI) + β_{age} × age + β_{sex} × sex]; ICV, intra-cranial volume; TBV, total brain volume; WM, sum of neo-cortical white matter; Frontal GM, frontal neo-cortical gray matter; Temporal GM: temporal neo-cortical gray matter; Parieto-occipital GM, parietal and occipital neo-cortical gray matter; MTL, medial temporal lobe.
[a]Includes supratentorial areas only.

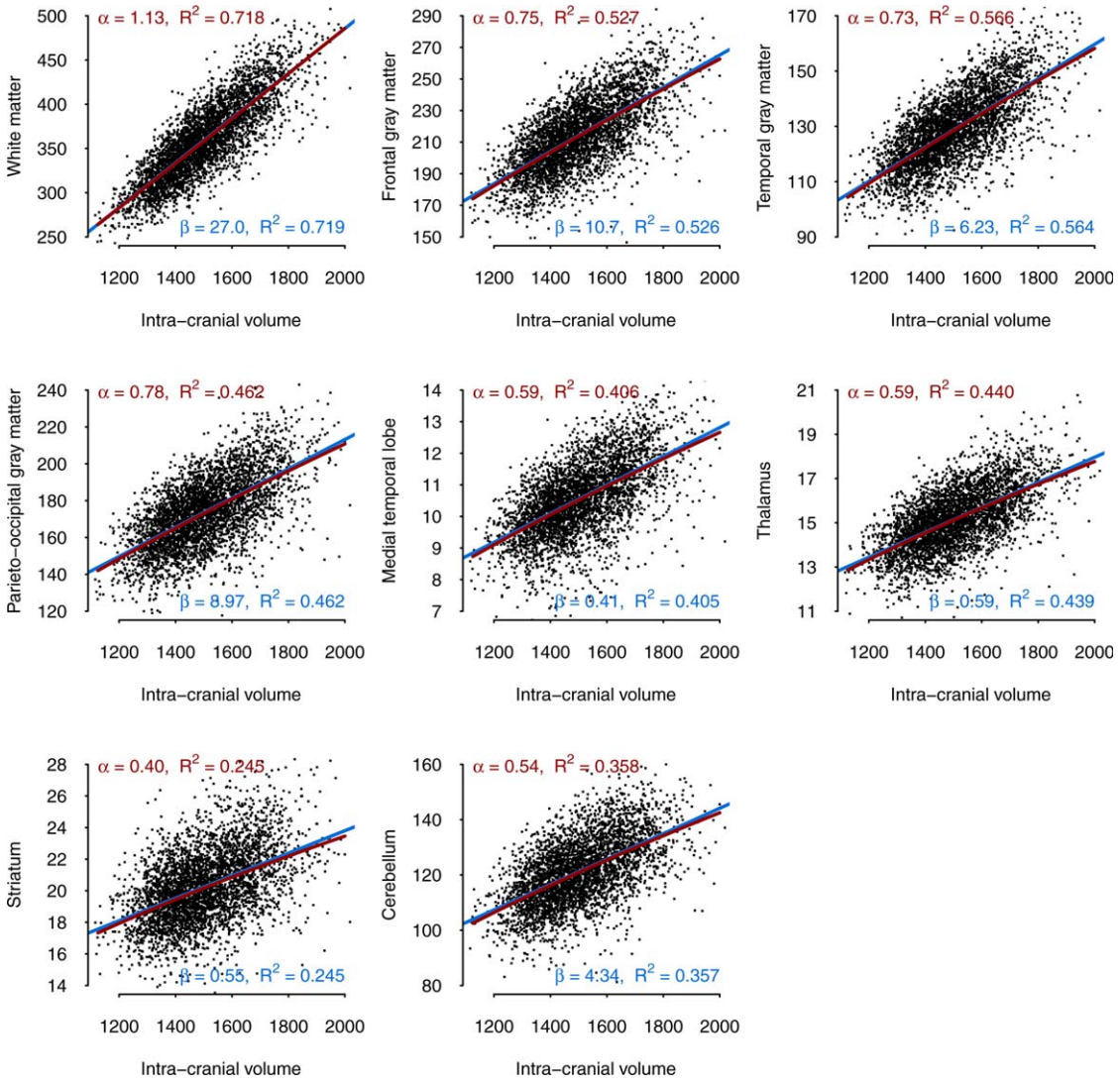

Figure 3.

Comparison of allometric log-log model to linear model of VOI to ICV. Red line, line of the allometric log–log model between the ICV and the VOI; Blue line, line of the linear model between the ICV and the VOI.

with those found in the AGES Reykjavik data. However, important differences were (1) allometric coefficients of the neo-cortical GM areas to ICV in CARDIA with values between 0.90 and 0.94 were higher, compared with those in the AGES and ADNI samples, and (2) WM volume in the ADNI data set seems to increase isometrically with ICV.

DISCUSSION

Different Allometric Scaling of Neo-Cortical WM, Neo-Cortical GM, and Deep GM

One goal of the present study was to assess and compare scaling coefficients of different VOIs to ICV in the AGES-Reykjavik dataset. We found all VOI to scale allometrically with ICV. One could roughly discern three patterns of scaling, that is, WM scaling, neocortical GM scaling and deep GM scaling. First, neo-cortical WM was the only structure to proportionally increase in larger ICV with a positive allometric coefficient of 1.14. Scaling coefficients of WM were found significantly different from all GM structures and cerebellum. Second, negative allometric coefficients were found for frontal (0.76), temporal (0.74), and parieto-occipital (0.79) cortical GM structures. Scaling coefficients of neo-cortical GM structures (frontal, temporal, and parieto-occipital) were not significantly different from each other, but were significantly larger than scaling coefficients of the deep GM structures when women and men were separately

assessed. Also scaling coefficients of MTL (0.60), thalamus (0.59), and the cerebellum (0.55) were not significantly different from each other in women and men separately. The scaling coefficient for striatal volume (0.41) was relatively invariant over the range of ICV and was significantly different from all other structures, except the cerebellum.

Allometric Scaling Cannot Solely Be Explained by Age, Sex, Ethnicity, or a Systemic Bias from Segmentation Pipeline

One important limitation of our study was that the sample consisted of older individuals, who have experienced various amounts of brain atrophy. Therefore, the observed scaling coefficients cannot be extrapolated to younger samples. After stratifying the AGES Reykjavik sample into quartiles of age, we found most structures to have similar scaling coefficients except for temporal GM (not including the MTL), which had lower α-coefficients in older individuals. We do not have an explanation for the significant difference in scaling found for temporal GM, but it prompted us not to rule out the possibility that allometric scaling of sub structures of the brain may vary with age in a way that we could not detect in the age span of our sample. Nonetheless, the findings of this article show that allometric scaling is a feature of the brain in the older population, which cannot be accounted for by adjusting for age when performing brain comparative studies.

A second important limitation was that all participants were Icelandic and the sample was genetically relatively homogeneous. Ancillary analyses in ADNI and CARDIA, with participants of younger age and different ethnicities, also showed that WM increased proportionally steepest with increasing ICV, followed by proportionally decreases in GM, with greatest decreases in the deep GM structures, similar to our observations in the AGES Reykjavik Study. Still, there were also differences in the results between the studies. The allometric coefficients of the cortical GM areas to ICV in CARDIA seemed higher compared those in the AGES and ADNI samples. A potential explanation could be that "ICV" in CARDIA was constructed from supratentorial structures only, and as a result allometric coefficients were higher. Another explanation could be that in the relatively young sample of the CARDIA allometric scaling is less pronounced. Further studies are needed to specifically examine this hypothesis. A second difference between the results of the additional analyses and our primary analyses in AGES was that WM volume in the ADNI data set seemed to increase isometrically with ICV. This may be explained by differences in tissue segmentation between GM and WM, as suggested by the higher mean volume of WM and lower mean volume of GM in ADNI compared with AGES Reykjavik. Depending on how border voxels are assigned to the GM and WM tissue classes, the difference between allometric coefficients may differ. Because of these differences in scaling coefficients among the study samples, it is at the moment not possible to establish fixed reproducible allometric coefficients for the human brain and more studies are needed.

A third potential limitation of the study was the use of an automated MR segmentation technique. Systematic errors, such as improper skull stripping, incorrect intensity thresholds, difficulty in segmenting sulcal CSF or imprecise template warping could all be possible sources of finding allometric correlations between VOI to ICV. However, when we fed artificially linearly scaled scans in the segmentation pipeline, the scaling coefficients of the output only showed small deviations from the isometric scaling law of 1, at maximum in the order of 2%. This could not explain the much larger deviations from 1 of the different scaling laws of VOI in the study sample. Therefore, we did not find evidence for a possible systematic error in the segmentation pipeline that could explain the allometry.

Allometric Scaling as True Feature of Brain Geometry

Differences in geometric or cyto-architectural properties of different brain structures may underlie differences and similarities in scaling to ICV. We observed similar scaling coefficients of different neo-cortical GM areas, which suggest they preserve proportionality to one another regardless of ICV. However, cortical GM and WM had significantly different scaling coefficients, indicating they do not preserve proportionality with varying brain size. This can be explained by differences in topology, where GM can be regarded as a surface of neural tissue covering an associated volume of WM [Dale et al., 1999]. The different lobes of the neo-cortex are similarly organized in repetitive cortical columns [Mountcastle, 1997]. Assuming a stable thickness of the neo-cortical GM "surface" across various brain sizes, as suggested by several studies [Hofman 1985; Hofman 1988; Mountcastle 1997], neo-cortical GM to WM should scale by an exponent of two-third (square-cube). If we focus on the results based on the AGES-Reykjavik study sample, we can observe that scaling coefficients of neo-cortical white to gray matter range from 0.65 to 0.70 (0.76/1.14 for frontal GM, 0.74/1.14 for temporal GM, and 0.79/1.14 for parieto-occipital GM), which approximates the geometric square-cube scaling law. Nevertheless, we did not establish the same results in the younger sample of CARDIA or the smaller sample of the ADNI and caution should be taken to apply a purely square-cube scaling law to the architecture of neo cortex. In a previous study slight increases of neo-cortical thickness (scaling of 0.2) with increase in ICV were observed [Im et al., 2008]. Another recent study showed the neocortical GM to have a more extensive gyrification, that is, to be "twistier," in larger brains compared with smaller ones [Germanaud et al., 2012]. Also, for other parameters, such as cell soma size or amount of supporting glial cells, the extent to which they vary with increasing brain size is

unclear. Some studies have also pointed to possible constraints in WM expansion, which should lead to scaling factors of white to gray that are higher than the square-cube law of two-third. It has been proposed that hemispheric specialization increases with increasing brain volume, which would lead to a decrease in inter-hemispheric connections and thus a decrease in WM volume [Ringo et al., 1994]. However, the coefficients reported in the present study for the AGES-Reykjavik study provide no evidence for such a limitation on WM expansion

The disproportionally lower scaling coefficients of deep GM structures to ICV compared with the cortex are not readily explained. The cortex gives rise to connections with striatum and thalamus, thus these structures could be expected to expand with neo-cortical GM volume. However, we found no evidence for preserved proportionality of the striatum and thalamus with cortical GM with scaling. Possibly, the deep GM structures are also influenced by other factors during brain development than neo-cortical growth. Brain structures grow in asynchronous patterns from birth through early adulthood and the striatum has been shown, together with frontal brain areas, to undergo more extensive developmental changes relatively late in early adulthood compared with other brain areas [Sowell et al., 1999]. Also, genetic factors could influence variation in regional brain volumes and lead to disproportional neo-cortical and deep GM volume increases with ICV, especially for the striatum. One twin study showed that the volume of the striatum, thalamus, and cerebellum were significantly more influenced by genetic factors compared with neo-cortical structures that were influenced more by environmental factors [Yoon et al., 2011]. And another twin-study concluded the phenotypic covariance of the striatal structures, hippocampus, and thalamus was primarily due to patterns of genetic covariance [Eyler et al., 2010].

Implications of Allometric Scaling for Methods of Head/Brain Size Adjustment

Knowledge on the allometric scaling of regional brain volumes is important for the discussion of adjustment methods for normal variation in comparative brain studies to volumetric and morphological changes. Allometric scaling implies both non-proportionality and non-linearity of scaling. Our results contribute to the understanding why certain methods should not be used. Ratios of brain structure volume over ICV or stereotaxic normalization by means of linear affine transformation assume isometric scaling of the brain, that is, proportionate scaling, which may lead to over- or underestimation of results. Therefore the use of these methods should be avoided, except when studying disproportionality is the purpose. The erroneous effect of linear spatial normalization on groups with differences in ICV was illustrated in a study comparing neo-cortical thickness differences in stereotaxic and native space between men and women [Luders et al., 2006]. The normalized data showed a disproportionately increased neo-cortical thickness in women compared with men, which was considerably attenuated in the unscaled data. Another important finding of our study was that allometric scaling was most apparent in deep GM structures. Unwanted effects of spatial registration therefore may be expected to be especially problematic in deep gray matter structures. Previously, a study reported that spatial-transformation based methods indeed produce significantly different proportions in smaller structures such as the hippocampus [Allen et al., 2008]. Lastly, we compared the fit of the allometric model to a linear model in predicting the relationship of VOI to ICV. We found very small differences in R^2, which implies the allometric model and linear model could substitute each other in the range of total brain size variation among humans. Therefore, we conclude that it is important in brain comparative studies to adjust for non-proportionality, but not for non-linearity.

CONCLUSION

In summary, our study found allometric scaling of WM, neo-cortical GM and deep GM structures to ICV in large samples of adult humans with different age, sex, and ethnicity. A positive allometric coefficient was found for WM and negative allometric coefficients for neo-cortical and deep GM structures, with smallest scaling coefficients for deep GM. Furthermore, our analysis showed that the allometric scaling cannot solely be explained by age, sex, ethnicity, or a possible systematic bias arising from the automated segmentation algorithm. We therefore conclude allometry is a true feature of the brain geometry.

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ADNI

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CARDIA

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